National Center for Computational Sciences Snapshot
The Week of September 10, 2007

<u>Next-Generation Pharmaceuticals Fight Brain Theft</u>

Researchers explore the effectiveness of Alzheimer's drugs' mechanisms

Biologists and materials scientists are using the Cray XT4 Jaguar supercomputer at Oak Ridge National Laboratory (ORNL) and other systems to discover the mechanisms by which a new type of Alzheimer's drug may stop the progression of Alzheimer's plaque formation and potentially disassemble the Alzheimer's fibrils, or fine filaments, that make up the plaques.

A team led by Ed Uberbacher of ORNL's Biosciences Division is performing first-principles calculations of Alzheimer's drugs and computing the molecular dynamics of these drugs combined with Alzheimer's fibrils to explore the mechanisms by which drug molecules attach to and reconfigure Alzheimer's peptides bound in fibrils. One promising compound developed by researchers now at Georgetown University and licensed by Samaritan Pharmaceuticals shows an ability to dramatically change the conformation of the Alzheimer's peptide when it is bound within a fibril.

The first step in the modeling process involves calculating an accurate force field for the drug itself. This involves ab initio (quantum mechanical) calculations of the chemical bonds and energies that hold the drug together.

"Since we can do quantum mechanical ab initio calculations on 1,000 atoms or so, we can generate this knowledge in a way that is more accurate than what pharmaceutical companies usually do," explains Phil LoCascio of ORNL. "Hopefully this method will become more widespread in industry and lead to better drug design."

In the computational simulation, 20 to 50 drug molecules are combined with a ten-peptide amyloid fibril system and allowed to interact with the fibril in a natural way for periods of ten to 100 nanoseconds. The results show a number of interesting phenomena, including interactions between the drugs and fibril surfaces. The drug molecules effectively cover the growing end of the fibril, potentially impeding any further growth. Furthermore, peptides in the fibril begin to disassociate from the fibril and assume conformations more like what they experience in solution. This work provides an initial model for how peptide dissociation from the fibril can be made to occur. The specific interactions between drug molecules and Alzheimer's peptides have provided clues to how to improve the drugs' design.

Researchers are planning simulations involving alternative drug compounds based on knowledge gained in these earlier simulations. They also intend to test mouse models of Alzheimer's disease with the University of Tennessee.

In addition to the impact on Alzheimer's disease, the ab initio and classical simulations being performed on Jaguar are important as a demonstration of a new paradigm for dynamically modeling drug-protein interactions. The methodology the team is developing will pave the way for researchers to simulate such interactions with much higher accuracy and may yield significant insight.

Radio Waves Are Hot Enough for ITER

Fusion researcher shows that when it comes to heating plasma, bigger is sometimes better

ORNL physicist Fred Jaeger has increased our confidence that radio-wave heating will work effectively in the multibillion-dollar ITER fusion reactor. ITER, a cooperative effort between nations in Europe and Asia as well as the United States, is being developed to demonstrate the scientific and technological feasibility of fusion power. If it succeeds, it promises to usher in an era of abundant, clean, and affordable energy.

The reactor will use radio waves to heat an ionized gas known as a plasma ten times hotter than the sun, thereby causing atoms in the gas to fuse and release energy. Analytical theory, one- and two-dimensional simulations, and experiments have provided an understanding of the relative success of radio-wave heating on medium-scale experiments and relative inefficiency on smaller experiments.

Using his AORSA application on ORNL's Cray XT4 Jaguar supercomputer, Jaeger was able to perform three-dimensional simulations for both present experiments and ITER. He verified that radio waves tended to heat the edge of the plasma instead of the center on smaller experiments. He also demonstrated, however, that radio heating should work efficiently in the larger ITER reactor, which measures more than 12 meters across and will hold more than 840 cubic meters of plasma.

Sharing High-Performance Computing's Promise with the Public

NCCS staffers discuss the facility's mission with the community, policymakers, and more

July marked a month of tireless outreach for Doug Kothe, director of science at the National Center for Computational Sciences (NCCS), and Bobby Whitten, NCCS senior user support specialist. "It's important for the public to know that we do what we do so we can keep America competitive and that there are advantages locally, regionally, nationally, and globally," Whitten said.

The nation's top energy researchers need high-performance computing to develop powerful models and simulations, Kothe told policymakers, program managers, and scientists July 10 in Washington, D.C., during a lecture series about emerging technologies. Speaking at the Department of Energy's Energy Efficiency and Renewable Energy program office, he shared ways scientists performing research in bioenergy, wind and solar power, and energy efficiency could work with the NCCS to infuse and advance their research with high-performance computing.

On July 17, Kothe's colleague Whitten delivered his fifth outreach talk of the year to the Sertoma service club in Knoxville, Tennessee. His prior talks addressed the Chattanooga

Engineer's Club, educational professionals affiliated with the University of Tennessee, Friends of Oak Ridge National Laboratory, and the Cray Users Group. In October he will address attendees at the Oklahoma Supercomputing Symposium in Norman, Oklahoma. His talks provide an overview of the NCCS, which is located at ORNL and grants time on supercomputers to 28 principal investigators whose projects explore grand challenges in climatology, physics, biology, and beyond.